REMARKS

This Reply is responsive to the non-final Office Action dated January 12, 2009. Reconsideration and allowance of the pending claims are respectfully requested in view of the amendments and remarks submitted herein.

I. Status of the Claims

At the outset, claims 104-140 have been canceled as they are directed to a nonelected invention. Claim 76 has been amended to incorporate the limitation from claim 77, and to clarify that transfection of the same double stranded RNA produced outside the cell induces an RNA stress response in the RNA stress response-competent cell when administered at a comparable level. Support for this amendment may be found on page 81, lines 7-25, which describes transfecting stress response competent cells with both an expression construct expressing a 600 bp dsRNA corresponding to a target gene, and a control dsRNA to the same target gene prepared *in vitro*, in comparable quantities (see also Figure 2). Claim 141 has been amended to depend on claim 76. No prohibited new matter has been added by way of these amendments.

II. Information Disclosure Statement

Applicants acknowledge with appreciation the Examiner's review of the Information Disclosure Statements. The missing documents will be submitted in due course, along with the requisite fee. Consideration of the additional documents is respectfully requested.

III. Rejection under 35 USC §112, Second Paragraph

Claim 76 and all dependent claims were rejected for alleged indefiniteness in view of the phrase "stress competent." According to the Action, one of ordinary skill in the art would not be able to determine the metes and bounds of this limitation and the phrase is allegedly absent from the specification. Applicants respectfully traverse.

The phrase used in claim 76 is actually "RNA stress response-competent" and finds support at the very least in Example 11, pages 80-85, of the specification. For example, on page 85, the specification states, "The cells that were used for these experiments were competent for RNA stress response induction as was demonstrated by the ability of cationic lipid complexed poly(I)(C) and *in vitro* transcribed RNA to induce/activate all tested components of this response." The indicators of an RNA stress response and the means to measure these indicators are disclosed in the paragraph bridging pages 80-81 and throughout the rest of Example 11 and include apoptosis as measured by the TUNEL assay, induction of alpha, beta and gamma interferon as detected by ELISA, activation of 2'5'OAS as measured by RNA fragmentation induction, PKR activation as measured by phosphorylation of EIF2alpha, anti-proliferative responses as measured by calculating the division rate of cells, and cytopathic effects as measured by microscopic analysis. Accordingly, the specification certainly describes the attributes of a RNA stress response-competent cell as well as assays to detect these attributes. Moreover, the stress response associated with double stranded RNA was well known prior to the present filing (i.e., see discussion at page 20 of the specification). The skilled artisan would clearly comprehend what makes a cell RNA stress response competent and would clearly be able to measure that competency based on the teachings of the specification. Reconsideration and withdrawal of the rejection under 35 USC 112, second paragraph are respectfully requested.

IV. Rejection under 35 USC §112, First Paragraph

Claims 76, 77, 79-82, 90, 91, 99, 100 and 141 were rejected as failing to comply with the written description requirement for allegedly containing new matter. According to the Action, the limitation "stress competent" is considered new matter because there is allegedly no reasonable description of this limitation, either literally or by way of example. Applicants respectfully disagree for the reasons discussed above in response to the 112, second paragraph rejection. The specification clearly describes the attributes of a RNA stress response-competent cell as well as assays to detect these attributes (see, e.g., Example 11, pages 80-85). Reconsideration and withdrawal of the rejection under 35 USC 112, first paragraph are respectfully requested.

V. Rejections under 35 USC §§102 and 103

Claims 76, 77, 79-81, 99, 100 and 141 were rejected under 35 USC §102(b) as being allegedly anticipated by Li et al. (US 2002/0114784, which published on August 22, 2002). At the outset, Applicants note that Li et al. is not a 102(b) reference since it was published well after Applicants' priority date of January 31, 2002, and Applicants are entitled to at least this priority date given the passages from the specification discussed above.[1]

In any case, according to the Office Action, the cells used in Li are considered to be stress response competent in light of the disclosure in Li at paragraph [0118]. It is not clear whether the cells used in Li were RNA stress response competent, but the fact that injection of a control double-stranded RNA at the same concentration as the target-specific dsRNA failed to cause any toxicity suggests that either the cells employed were not competent to mount an RNA stress response, or the amount of double stranded RNA administered to the cells was too low to mediate interferon-mediated toxicity, as postulated in Li in paragraph [0118].

In that regard, Applicants have amended claim 76 above to clarify that, in the methods of the present invention, transfection of the same double stranded RNA produced outside the cell will induce an RNA stress response in the RNA stress response-competent cell when administered at a comparable level. Indeed, Applicants have shown that transfection of a target-specific dsRNA made in vitro, as well as non-specific poly(I)(C)RNA, induced a RNA stress response in stress response competent human rhabdomyosarcoma cells, whereas transfecting a comparable quantity of expression vector encoding and expressing the same dsRNA did not result in a RNA stress response and moreover resulted in a 95% reduction in target gene expression (see pages 78 and 81). Further, Applicants note that the amount of target-specific dsRNA being supplied to the cell by way of an expression vector is actually much higher than the mere quantity of nucleic acid administered since cells receiving the expression vector will have the capability of continuously producing more dsRNA, in contrast to the situation where dsRNA is administered directly to a cell.

Li does not disclose a method of downregulating expression of a target gene in an RNA stress response-competent cell by administering an expression vector encoding a double stranded

[1] Applicants believe they are also entitled to the benefit of the filing date of the provisional applications.

RNA corresponding to the target gene, wherein transfection of the same double stranded RNA produced outside the cell induces an RNA stress response in the RNA stress response-competent cell when administered at a comparable level, as is now recited in amended claim 76. In fact, as stated in paragraph [0118] of Li, "injection of control double-stranded RNA at the same concentration does not cause a detectable deviation from the wild type expression levels or phenotype." Moreover, Li actually teaches away from in-cell expression of dsRNA given that Li teaches that the amount of dsRNA administered to a vertebrate cell must be tightly controlled in order to avoid an interferon stress response. The skilled artisan would not be motivated to try in-cell expression of target-specific dsRNA in view of the Li disclosure, since Li provides no direction for how to control the amount of dsRNA delivered to the cell by vector expression.

In light of the amendments and arguments presented above, reconsideration and withdrawal of the rejection under 35 USC §102(b) based on Li et al. are respectfully requested.

Claims 76, 77, 79-82, 90, 91, 99, 100 and 141 were rejected under 35 USC §103(a) as being allegedly unpatentable over Fire (WO99/32619) and Wianny (Nat. Cell Biol. 2:70-75, 2000), and optionally Li et al. (2002/0114784). According to the Office Action, the cells employed in Fire et al. are "stress competent" because they may be tested for stress in response to an environmental condition. This is not the same, however, as being "RNA stress response competent" as recited in the instant claims, which specifically relates to the PKR- or interferon-associated toxicity of dsRNA toward vertebrate or mammalian cells. The invertebrate cells employed by Fire were certainly not RNA stress response competent. Indeed, even Fire expressed doubts publicly that RNA interference could be used in mammalian cells in view of the double-stranded RNA-mediated PKR stress response.

For example, in 1998 after Fire and Mello filed their patent application, Fire stated, "Any gene-specific interference by dsRNA in PKR-proficient mammalian cells would be dependent on a transient lapse in the PKR response, or on a controlled level of dsRNA that was incapable of activating PKR" (TIG 1998, 14(7): 255-58, at p. 258, col. 2, attached). Thus, prior to Applicants' disclosure, the skilled artisan working in the RNAi field would not have believed that specific inhibition of gene expression could be accomplished in stress response-competent

vertebrate cells using dsRNA. In particular, the skilled artisan would not have believed that specific inhibition of gene expression could be accomplished in stress response-competent vertebrate cells using long dsRNA that is over 30 base pairs long. This is evidenced by several articles published after Applicants' priority date of January 31, 2001, which show that those of skill in the field of RNA interference did not believe that RNAi could be accomplished in vertebrate cells that were capable of mounting an interferon response.

For example, the attached article by Billy *et al.*, published in December 2001, shows that those of skill in the RNAi field at that time believed that both long and short dsRNA molecules could be used to produce RNAi in invertebrate animals, but that long dsRNAs produce non-specific toxicity in differentiated vertebrate cells due to the interferon response (see Introduction section on page 14428-33). In fact, based on the disclosure of Billy *et al.*, the skilled artisan would have believed that RNAi in vertebrate cells is only possible where the cells are deficient in the interferon response. This prejudice is reiterated by Diallo *et al.* in 2003 (Abstract attached), who provided one of the first reports in a scientific journal that long, endogenously expressed dsRNA can be used to mediate RNAi in mammalian cells in the absence of an interferon response.

Thus, Fire fails to teach target-specific inhibition of gene expression in RNA stress response competent cells. Moreover there was a prejudice in the art at the time of the invention that RNA interference could be readily applied to RNA stress response competent cells, a prejudice that was advanced by Fire himself. Applicants have overcome this prejudice in the art concerning the use of dsRNAs, and particularly long dsRNAs, to mediate RNA interference in vertebrate cells. To Applicants' knowledge, they were the first to describe the successful practice of RNAi in RNA stress response-competent vertebrate cells using endogenously expressed dsRNA.

Li *et al.* does not overcome the prejudice in the art concerning the use of dsRNAs to mediate RNA interference in stress-response vertebrate cells, since the cells actually exemplified in this application were either deficient in the RNA stress response, or Li employed a controlled level of dsRNA that is incapable of inducing a RNA stress response and not amenable to endogenous expression systems. Moreover, Li actually teaches away from in-cell expression of dsRNA as claimed given that Li teaches that the amount of dsRNA administered to a vertebrate cell must be tightly controlled in order to avoid an interferon stress response. The skilled artisan

would not be motivated to try in-cell expression of target-specific dsRNA in view of the Li disclosure, since Li provides no direction for how to control the amount of dsRNA delivered to the cell by vector expression.

Wianny *et al.* also do not overcome the prejudice in the art concerning the use of RNAi in vertebrate cells, because Wianny *et al.* merely show the practice of RNAi in vertebrate embryonic cells that were already known in the art to be deficient in the interferon response. In this regard, it has been known in the art since at least the 1970s that vertebrate embryonic cells are deficient in the interferon response. For instance, as stated in Haggarty *et al.* (1988, Nucleic Acids Res. 16(22): 10575-92, copy attached), one of the markers associated with the undifferentiated state of embryonal carcinoma (EC) cells is "the inability to produce interferon in response to exposure to viruses or double stranded RNA, a characteristic shared with early embryos" (with emphasis). In fact, Haggarty *et al.* cites several articles published between 1978-1984 that show that, even then, it was known that vertebrate embryonic cells do not produce or respond to interferon. See Burke, 1978, Cell 13:243-48; Barlow *et al.*, 1984, Differentiation 27:229-35 (copies attached).

Thus, Wianny *et al.* also fail to teach or render obvious the claimed invention and fail to overcome the prejudice in the art concerning the use of RNAi in vertebrate cells, because Wianny *et al.* merely show the practice of RNAi in vertebrate embryonic cells that were already known in the art to be deficient in the interferon response as discussed above. Accordingly, Wianny does not make up for the deficiencies of either Fire or Li. The public statements of Fire coupled with the state of the art at the time of the invention suggest that one of ordinary skill in the art would not have had a reasonable expectation of success in arriving at the claimed invention. Reconsideration and withdrawal of the rejection under 35 USC §103(a) are respectfully requested.

Except for issue fees payable under 37 CFR §1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. 1.16 and 1.17 which may be required, including

any required extension of time fees, or credit any overpayment to Deposit Account 50-1283. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. 1.136(a)(3).

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Respectfully submitted,
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